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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/524,343	01/30/2006	Andrzej Lipkowski	7444/73871/GJG	4648
23432	7590	06/06/2008		
COOPER & DUNHAM, LLP 1185 AVENUE OF THE AMERICAS NEW YORK, NY 10036			EXAMINER	
			HA, JULIE	
			ART UNIT	PAPER NUMBER
			1654	
MAIL DATE	DELIVERY MODE			
06/06/2008	PAPER			

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

**Advisory Action  
Before the Filing of an Appeal Brief**

**Application No.**

10/524,343

**Applicant(s)**

LIPKOWSKI ET AL.

**Examiner**

JULIE HA

**Art Unit**

1654

**–The MAILING DATE of this communication appears on the cover sheet with the correspondence address –**

THE REPLY FILED 01 May 2008 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1.  The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a)  The period for reply expires 4 months from the mailing date of the final rejection.  
 b)  The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.  
 Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**NOTICE OF APPEAL**

2.  The Notice of Appeal was filed on \_\_\_\_\_. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

**AMENDMENTS**

3.  The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because  
 (a)  They raise new issues that would require further consideration and/or search (see NOTE below);  
 (b)  They raise the issue of new matter (see NOTE below);  
 (c)  They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or  
 (d)  They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: \_\_\_\_\_. (See 37 CFR 1.116 and 41.33(a)).

4.  The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).

5.  Applicant's reply has overcome the following rejection(s): \_\_\_\_\_.

6.  Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

7.  For purposes of appeal, the proposed amendment(s): a)  will not be entered, or b)  will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: \_\_\_\_\_

Claim(s) objected to: \_\_\_\_\_

Claim(s) rejected: 2,3,5-9 and 17

Claim(s) withdrawn from consideration: 11-16 and 18-23.

**AFFIDAVIT OR OTHER EVIDENCE**

8.  The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).

9.  The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fail to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).

10.  The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

**REQUEST FOR RECONSIDERATION/OTHER**

11.  The request for reconsideration has been considered but does NOT place the application in condition for allowance because:  
 Please see continuation page.

12.  Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). \_\_\_\_\_

13.  Other: \_\_\_\_\_

/J. H./  
 Examiner, Art Unit 1654

/Anish Gupta/  
 Primary Examiner, Art Unit 1654

## 11 Continuation:

Claims 2-3 and 6-8 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Ronai et al in view of Abbruscato et al and Kanai et al as for reasons set forth in the previous office action.

Applicant argues that the modifications to the prior art proposed have unpredictable effects, and were known to be unpredictable by those skilled in the art. Applicant argues that "the very wording of the rejection 'to see what effect' acknowledged the unpredictability of the prosed modification." Applicant argues that the Kanai et al reference "discusses in addition to methionine, the amino acids leucine, isoleucine, valine, phenylalanine, tyrosine, tryptophan and histidine, and there were other amino acids that were transported at higher rates than methionine." Furthermore, Applicant argues that "Ronai et al illustrate the unpredictability of altering termini and altering residues...sometimes opposite effects in mouse vs deferens and guinea pig ilem." Applicant further argues that there is no suggestion in the combination of the cited prior art to make a dimeric peptide analog of enkephalin; Abbruscato et al teaches away from those claimed dimeric compounds listed in claim 2 that do not contain phenylalanine. Additionally, Applicant argues that there is unpredictability to modify the two amino acids (replacing D-Ala in position 2 of biphalin with D-Thr)...the biological consequence of such double substitution is not predictable.

Applicant's arguments have been fully considered but have not been found persuasive. As indicated in the previous office action, Ronai teaches the monomer of Tyr-D-Met-Gly-Phe-NH<sub>2</sub> and Abbruscato teach the compound biphalin (Tyr-D-Ala-Gly-Phe-NH)<sub>2</sub>, and has shown that biphalin has been shown to be more potent than morphine and capable of crossing the BBB. Since Abbruscato et al teach the dimerization of a well known pharmacophore (enkephalin) and shows the increased potency and crossing the BBB capability, it would have been obvious to combine the teachings, and make a dimer of Tyr-D-Met-Gly-Phe-NH, since Ronai et al indicate the increase in potency of this monomer. Furthermore, Kanai teaches the affinity to methionine. Kanai et al teach a limited number of amino acids (8 including methionine), and methionine worked as well as the other amino acids (except for Phe and Trp). Therefore, it would have been obvious to combine and one of ordinary skill in the art would have been motivated to combine, since the biphalin has greater potency and crossed BBB. Further, Ronai et al indicate decrease of potency in MVD but not in GPI, and this indicates that the enkephalin agonists are specific towards different species. The unpredictability argument cited in page 13 of Applicant's remark do not compare two of the same sequences. The first monomer opioid sequence Applicant cites has the sequence Tyr-Gly-Gly-Phe-Leu-Arg-Ile-Arg-Pro-Lys, and the dimer sequence is Tyr-D-Ala-Gly-Phe-NH-Phe-Gly-D-Ala-Tyr. Only looking at the Tyr-Gly-Gly-Phe of the first sequence, only Gly of so called "message" is replaced with D-Ala. Applicant indicated that modification in the "message" portion tends to influence potency of the analogue whereas modification in "address" portion mainly modulates receptor selectivity. Thus, looking at the peptide sequence of Ronai et al (Tyr-D-Met-Gly-Phe-NH<sub>2</sub>), the "message" portion would be D-Met-Gly area. Thus, modification of D-Met would give two amino acid substitutions both at the "message" positions. Since the enkephalin disclosed by Ronai et al had greater potency, and biphalin disclosed by Abbruscato et al showed increased potency and crossed BBB, there is a reasonable expectation that dimerizing the enkephalin of Ronai would have increased potency and ability to cross BBB. Applicant is reminded that Applicant elected sequence Tyr-D-Met-Gly-Phe dimeric sequence. If a prior art is found that anticipates or renders obvious the elected species, the prior art search will not be extended unnecessarily to cover all non-elected species (see MPEP 803.02). Therefore, Applicant's argument that the Abbruscato reference teaches away from the biphalin sequences that do not contain phenylalanine is moot.

Claims 2-3 and 5-9 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Ronai et al in view of Abbruscato et al and Kanai et al in further view of Hill et al, Bock et al and Ornstein for the reasons set forth in the previous office action.

Applicant argues that "the teachings of Hill et al., Bock et al. and Ornstein do not cure the deficiencies of Ronai et al, Abbruscato et al and Kanai et al. The combination of references does not teach or suggest applicant's invention."

For the reasons provide above and cited in the previous office action, the combined prior arts are obvious over the instant claims.

Applicant further indicates that "the present application is a 371 national stage of PCT/PL2003/00077. According to MPEP 609.03, the Examiner has considered "the documents cited in the international search report in a PCT national stage application when the FORM PCT/D/EO/903 indicates that both the international search report and the copies of the documents are present in the national stage file... Examiner has listed the first document, Lipiowski et al (1999) on the form PTO-892. Applicant notes that the second document, Lipiowski et al (2002) has not been listed in a PTO-892 by the Examiner. For completeness of the record, and in accordance with MPEP 609, Applicant attach hereto as Exhibit B a substitute form PTO-1449 listing Lipiowski et al, and respectfully request that the Examiner initial and return a copy of the form to the undersigned."

Applicant is noted that no Information Disclosure Statement (IDS, PTO-1449) was filed with the 371 National stage application, nor copies of these references provided. The only reason the Examiner of record cited the reference in the PTO-892 was because the Examiner used the reference as prior art. If a IDS was filed, the references disclosed would have been considered, and the PTO-1449 would have been initialed and signed and a copy returned to the undersigned. However, since IDS and references were not provided, the second Abbruscato reference (2002) that was listed on the search report, may have been considered, but only cited in the PTO-892 if the reference was used as a prior art. Since the reference was not used as a prior art, this reference was not cited. Furthermore, the IDS filed with Applicant's Arguments/Remarks on May 01, 2008 has not been considered, since Applicant did not provide a copy of the reference.

## Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JULIE HA whose telephone number is (571)272-5982. The examiner can normally be reached on Mon-Thurs, 5:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system.

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/J. H./  
Examiner, Art Unit 1654